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(71) Applicant: UNILEVER PLC
Unilever House Blackfriars P.O. Box 68
London EC4P 4BQ (GB)

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(71) Applicant: UNILEVER NV
Burgemeester s'Jacobplein 1 P.O. Box 760
NL-3000 DK Rotterdam (NL)

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(72) Inventor: Scott, Ian Richard
6 Heylake
Wellingborough Northants NN8 3NZ (GB)

(74) Representative: Tonge, Robert James et al
UNILEVER PLC Patents Division P.O. Box 68 Unilever House
London EC4P 4BQ (GB)

(54) Skin treatment composition.

(57) A composition for topical application to mammalian skin comprises hyaluronic acid fragments comprising from 7 to 50 monosaccharide units terminating either with a glucuronic acid unit and/or a N-acetyl glucosamine unit, or an unsaturated derivative of one or both of these terminal units and a cosmetically acceptable vehicle.
provide that when the fragments of hyaluronic acid consist essentially of fragments composed of more that 26 monosaccharide units, then the composition also comprises a means for enhancing the activity of said fragments of the composition in terms of angiogenic and/or hair growth response, following topical application to the skin

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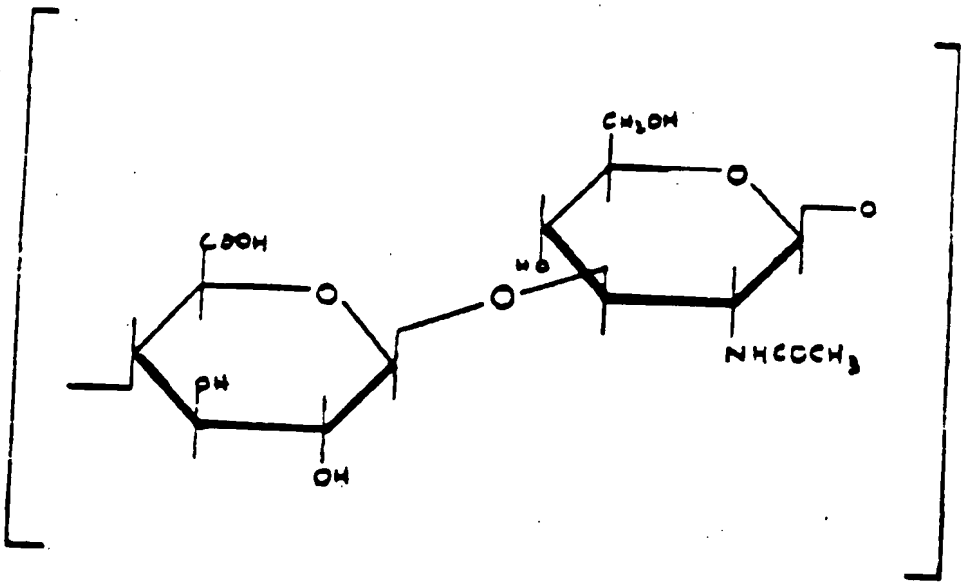
DISCLOSURE OF THE INVENTION

The fragments of hyaluronic acid

The composition according to the invention comprises fragments of the glycosaminoglycan derivative hyaluronic acid.

Hyaluronic acid itself consists of repeating units of glucuronic acid and N-acetyl glucosamine, having the structure (1):



(1)

The fragments of hyaluronic acid are characterised as polysaccharides containing from 7 to 50 monosaccharides terminating either with a glucuronic acid unit and/or an N-acetyl glucosamine unit, or an unsaturated derivative of one or both of these terminal units.

It is apparent the the larger the fragments of hyaluronic acid, the greater the difficulty there is in delivering the fragments to the dermal layer of the skin, unless there is also present in the composition a means for enhancing the activity of said fragments. Accordingly, the preferred fragments of hyaluronic acid are polysaccharides containing from 7 to 26 monosaccharide units

These fragments can be obtained by digestion of hyaluronic acid with the enzyme hyaluronidase, or by chemical cleavage of hyaluronic acid or by chemical synthesis from monosaccharides, disaccharides or short chain polysaccharides. The amount of of hyaluronic acid fragments to be incorporated in the composition according to the invention can be determined either by an angiogenic response, or by a hair growth response. Accordingly, when the fragments are to be employed in the area of skin benefit, the amount of the said fragments of hyaluronic acid present in the composition will be at least sufficient, after a period of at least 5 days, to increase the development of blood vessels in the skin of the rat the animal model selected for this test, when said composition is applied topically to the skin, by at least 5% more than that obtainable using a control composition from which the said fragments have been omitted

Preferably, the amount of said fragments should be sufficient to increase the development of blood vessels in the skin of the rat by this technique by at least 10%, more preferably by at least 25%, most preferably by at least 40% and ideally by at least 50%.

Alternatively, when the fragments of hyaluronic acid are to be employed in stimulating hair growth or regrowth, the amount of said fragments present in the composition according to the invention will be at least sufficient, after a period of at least 14 days, to increase hair growth in the rat, the animal model selected for this test, when said composition is applied topically to the skin, by at least 10% more than that obtainable using a control composition from which the said fragments have been omitted.

Preferably, the amount of said fragments of hyaluronic acid should be sufficient to increase hair growth in the rat by at least 20%, more preferably by at least 30%, most preferably by at least 40% and ideally by at least 50%.

The sufficient amount will depend on the effectiveness of the fragments some being more effective than others, but in general, an amount of from 0.01 to 99%, preferably from 0.1 to 20% by weight of the composition will provide an adequate dose to mammalian, particularly human skin or hair following topical application.

The Vehicle

The composition according to the invention also comprises a solid, semi-solid or liquid cosmetically and/or physiologically acceptable vehicle, to enable the fragments of hyaluronic acid to be conveyed to the skin or hair at an appropriate dilution. The nature of the vehicle will depend upon the method chosen for topical application of the composition to the skin. The vehicle can itself be inert or it can possess physiological or pharmaceutical benefits of its own.

It should be explained that vehicles are substances which can act as diluents, dispersants or solvents for the fragments of hyaluronic acid which therefore ensure that if they can be applied to and distributed evenly over the hair and/or scalp at an appropriate concentration. The vehicle is preferably one which can aid penetration of the fragments of hyaluronic acid into the skin to reach the dermal layer of the skin. Compositions according to the invention can include water as a vehicle, and/or at least one cosmetically acceptable vehicle other than water.

Vehicles other than water that can be used in compositions according to the invention can include liquids or solids as emollients, solvents, humectants, thickeners and powders. Examples of each of these types of vehicles, which can be used singly or as mixtures of one or more vehicles, are as follows.

Emollients, such as stearyl alcohol, glyceryl monoricinoleate, glyceryl monostearate, propane-1,2-diol, butane-1,3-diol, mink oil, cetyl alcohol, isopropyl isostearate, stearic acid, isobutyl palmitate, isocetyl stearate, oleyl alcohol, isopropyl laurate, hexyl laurate.

Solvents, such as ethyl alcohol, methylene chloride, isopropanol, castor oil, ethylene glycol monoethyl ether, diethylene glycol monobutyl ether, diethylene glycol monoethyl ether, dimethyl sulphoxide, dimethyl formamide, tetrahydrofuran;

Humectants, such as glycerin, sorbitol, sodium 2-pyrrolidone-5-carboxylate, soluble collagen, dibutyl phthalate, gelatin;

Powders, such as chalk, talc, fullers earth, kaolin, starch, gums, colloidal silicon dioxide, sodium polyacrylate, tetra alkyl and/or trialkyl aryl ammonium smectites, chemically modified magnesium aluminium silicate, organically modified montmorillonite clay, hydrated aluminium silicate, fumed silica, carboxyvinyl polymer, sodium carboxymethyl cellulose, ethylene glycol monostearate.

The amount of vehicle in the composition, including water if present, should preferably be sufficient to carry at least a portion of the fragments of hyaluronic acid to the skin in an amount which is sufficient effectively to enhance skin quality or hair growth. The amount of the vehicle can comprise the balance of the composition, particularly where little or no other ingredients are present in the composition. Accordingly, the vehicle or vehicles can comprise from 1 to 99.99%, preferably from 50 to 99.5% and ideally from 90 to 99% by weight of the composition.

Activity Enhancer

The composition according to the invention also preferably comprises a means for enhancing the activity of the fragments of hyaluronic acid, especially to improve their penetration through the skin following topical application, with the consequence that skin benefit can be further improved and where appropriate hair growth enhanced.

It is accordingly apparent that the larger fragments of hyaluronic acid, that is those comprising more than 25 monosaccharide units, are too large to penetrate the skin to any significant extent unless there is also present an activity enhancer. Smaller molecular fragments of hyaluronic acid that is those comprising from 7 to 25 monosaccharide units penetrate the skin more readily, but nonetheless their penetration can also be substantially enhanced in the presence of an activity enhancer.

The activity enhancer can be chosen from a wide variety of molecules which can function in different ways to enhance the benefits of the fragments of hyaluronic acid. Particular classes of activity enhancers include hair growth stimulants other than the said fragments, penetration enhancers and cationic polymers, whose presence can further improve the delivery of the fragments through the stratum corneum to their site of action. Some activity enhancers can also function as vehicles for the fragments of hyaluronic acid.

The means for enhancing the activity of the fragments of hyaluronic acid can also take the form of an iontophoretic device as will be explained later. This and other means for enhancing the activity of the said fragments are now disclosed in greater detail.

(a) Other Hair Growth Stimulants

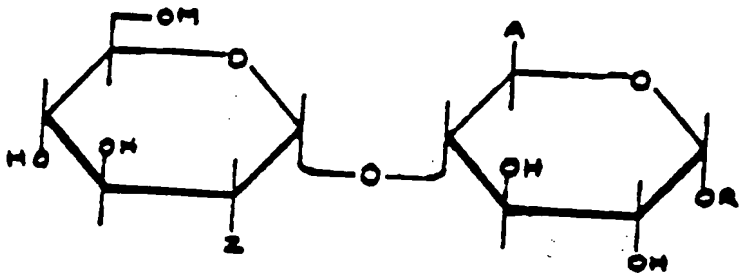
Examples of substances other than the fragments of hyaluronic acid substances which as activity enhancers themselves possess the ability to stimulate or increase hair growth include, for example:

Benzalkonium chloride
Benzethonium chloride
Phenol
Estradiol
Diphenhydramine hydrochloride
Chlorpheniramine maleate
Chlorophyllin derivatives
Cholesterol

Salicylic acid
Cystine
Red pepper tincture
Benzyl nicotinate
dl-Menthol
Peppermint oil
Calcium pantothenate
Panthenol
Castor oil
Hinokitiol
Prednisolone
Resorcinol

Further substances which themselves possess the ability to increase the rate of terminal hair growth include:

(i) α-1,4 esterified disaccharides described by Chosy S.A. in EP-A-0 064 012, having the structure (2):



(2)

where

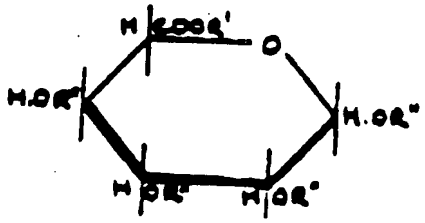
Z represents a functional nitrogen group, such as an azide or a group having the structure -NHB, in which B represents -H or a functional group such as acetyl or sulphate as a salt with an organic or mineral cation;

M represents -H or SO_3M_1, where M_1 is an organic or metallic cation, particularly an alkali metal; or an acetyl group;

R represents a C_1 to C_4 alkyl radical, especially methyl; or an aryl radical;

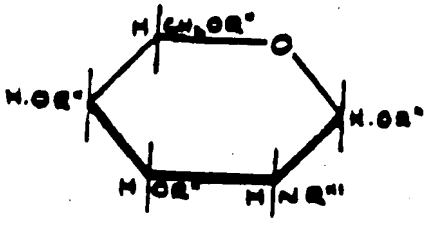
A represents a functional group such as an acid or $-COOR_1$, where R_1 represents -H or a C_1 to C_4 alkyl radical, especially methyl; or a metal, especially an alkali metal;

(ii) esterified oligosaccharides as described by Unilever in EP-A-0 211 610, including at least one esterified disaccharide unit consisting of a uronic acid residue having the structure (3):



(3)

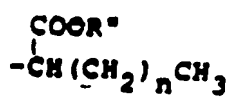
and a hexosamine residue having the structure (4):



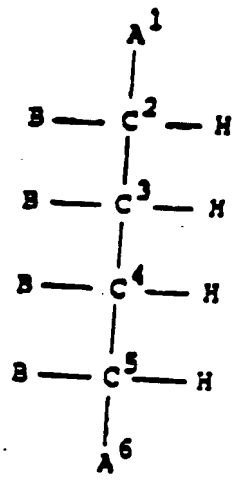
(4)

where

R' is -H, C3 to C_{10} alkyl or



R'' is -H, C_1 to C_4 alkyl, $-CO(CH_2)_mCH_3$, $-SO_3M$,
R''' is -H, $-CO(CH_2)_mCH_3$, or $-SO_3M$,
M is -H, or a metallic or organic cation
n is 0 or an integer of from 1 to 7, and
m is 0 or the integer 1 or 2;
the groups designated R'' being the same or different, one R'' group from each pyranose ring structure being linked by a glycosidic linkage having the configuration α-1,3, α-1,4, β-1,3 or β-1,4 and the $-COOR'$, $-CH_2OR''$ and $-OR''$ groups being of either configuration with respect to the pyranose rings,
(iii) Minoxidil and its derivatives, as described by The Upjohn Co in GB 1 187 736,
(iv) Minoxidil glucuronides, as described by Unilever in EP-O 242 967,
(v) Minoxidil sulphates, as described by The Upjohn Co. in WO 86/04231,
(vi) Direct proteoglycanase inhibitors, such as 1,10-phenanthroline,
(vii) Glycosaminoglycanase inhibitors, such as aldonolactones and esterified aldonolactones having the structure (5)



(5)

where
A^1 and A^6 are -H, $-CH_2-$, $-\overset{OR'}{\underset{|}{C}}=O$ or $-\overset{OR}{\underset{|}{C}}=O$
B is OR'' or a lactone linkage to position 1 or 6, or $-NHCOCH_3$
and where
R is -H or C_2 to C_6 alkyl,
R' is the remainder of the molecule joined through another C atom at positions 2 to 5 to form a lactone,
R'' is -H or C_2 (ie acetyl) to C_4 acyl of either configuration with respect to the backbone of the molecule;
preferred examples of which include:
L-Galactono-1,4-lactone
L-Arabino-1,5-lactone
D-Fucono-1,5-lactone
D-Glucaro-1,4-lactone
D-Glucurono-6,3-lactone
Galactaric acid lactone
2-Acetamido-2-deoxygluconolactone
2-Acetamido-2-deoxygalactono-lactone
D-Glucaro-1,4:6,3-dilactone
L-Idaro-1,4-lactone